IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

PERNIX IRELAND PAIN DAC and PERNIX THERAPEUTICS, LLC,	)	
Plaintiffs,	)	
v.	)	C.A. No. 16-139-WCB
ALVOGEN MALTA OPERATIONS LTD.,	)	
Defendant.	)	

BRIEF IN OPPOSITION TO PLAINTIFFS' MOTION FOR SUMMARY JUDGMENT OF NO INVALIDITY UNDER 35 U.S.C. § 101

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TABLE OF CONTENTS

Page

TABLE OF AUTHORITIES

Page(s)

Cases

Statutes

Defendant Alvogen Malta Operations Ltd. respectfully submits this Opposition to Plaintiffs Pernix Ireland Pain DAC's and Pernix Therapeutics, LLC's (collectively, "Pernix") Motion for Summary Judgment that claims 1-4, 11, 12, 17 and 19 of U.S. Patent No. 9,265,760 ("the '760 patent") and claim 1 of U.S. Patent No. 9,339,499 ("the '499 patent") (collectively, "the Asserted Claims") are not invalid under 35 U.S.C. § 101. The parties agree that no genuine issue of material fact precludes entry of summary judgment under 35 U.S.C. § 101. The Court should, however, enter summary judgment for Alvogen, not Pernix.

I. NATURE AND STAGE OF THE PROCEEDINGS

This is a patent action under the Hatch-Waxman Act related to Alvogen's submission of ANDA No. 206986 for hydrocodone extended-release ("ER") tablets. Pernix asserts that Alvogen's ANDA Product will infringe the Asserted Claims. The parties have filed cross-motions for summary judgment under 35 U.S.C. § 101. (D.I. 111 and 114.) Alvogen submits this brief in opposition to Pernix's motion, and respectfully submits that this Court should grant Alvogen's Motion For Summary Judgement of Invalidity Under 35 U.S.C. § 101 ("Alvogen's § 101 Motion").

II. SUMMARY OF THE ARGUMENT

Each and every limitation recited by the Asserted Claims in this case, outside the natural law itself, constitutes "mere empty language." At least that is the way Pernix characterized its Asserted Claims to convince the Court that the non-adjustment step (which reflects the natural law) was an affirmative limitation of the claims. (D.I. 65 at 4-5.) The Asserted Claims are "directed to" this natural law and are otherwise conventional, i.e., "mere empty language." The named inventors did nothing more than administer a prior art hydrocodone dosage form and claim the human body's natural reaction to that dosage form in patients with and without hepatic impairment ("HI").

In accordance with the Federal Circuit's "directed to" standard, a natural law is thus the "focus" of the Asserted Claims and the only possible "alleged advance" relative to the prior art. Indeed, Pernix's brief in support of its Motion (D.I. 116, "Pernix's § 101 Motion") does not dispute the following key facts:

- The non-adjustment limitation in claims 1-4 and 11 of the '760 patent and the pharmacokinetic ("PK") values in claims 12, 17 and 19 of the '760 patent and claim 1 of the '499 patent recite and restate a natural law in the form of the relationship between HI and the bioavailability of hydrocodone in the body after administration of certain, known hydrocodone ER formulations;

- The specifications of the Patents-In-Suit characterize the "basic concept" of the alleged invention as this natural law; and

- The Patent Office's Reasons for Allowance of the '760 patent point to a restatement of this natural law, i.e., non-adjustment of the starting dose in patients with mild or moderate HI, as the basis for allowance.[1]

Recognizing these undisputed facts, Pernix seeks to sidestep the Federal Circuit's "directed to" legal standard. Pernix first asks this Court to create a new and unprecedented rule of law holding that all method of treatment claims are *per se* patent eligible. Pernix's position is legally unsupported and in direct conflict with decisions by multiple judges in this district. Next, Pernix inconsistently argues that the Asserted Claims are "directed to" two separate and distinct alternatives – (1) methods of treating pain and (2) administering a non-naturally occurring hydrocodone active. There is, of course, no evidence that the claims are directed to either of these alternatives, i.e., that either is the "focus" or "alleged advance" of the Asserted Claims, and Pernix offers none.

Nor can Pernix dispute that limitations outside the natural law itself are conventional. In fact, Pernix does not seriously argue that the Asserted Claims reciting pharmacokinetic ("PK")

[1] Notwithstanding the Reasons for Allowance, the natural laws themselves are also conventional.

values alone (claims 12, 17 and 19 of the '760 patent and claim 1 of the '499 patent) recite unconventional limitations. Instead, Pernix relies exclusively on non-adjustment of the starting dose, which is not even a limitation of claims 12, 17 and 19 of the '760 patent and claim 1 of the '499 patent. Regardless, it is well-settled that a natural law itself, like the non-adjustment limitation, cannot furnish the inventive concept necessary to establish patent-eligibility. And because Pernix admits that all remaining limitations constitute "mere empty language," these limitations cannot qualify as unconventional and inventive. As set forth more fully in Alvogen's § 101 Motion, they are conventional as a matter of fact. (D.I. 112 at 12-15.) Finally, Pernix's contention that this Court held on an incomplete record during Markman that non-adjustment of the starting dose was unconventional misconstrues and misapplies the "law of the case" doctrine.

Accordingly, all of Pernix's Asserted Claims are "directed to" natural laws and lack an inventive concept. They are invalid as patent ineligible under 35 U.S.C. § 101.

III. FACTUAL BACKGROUND

Alvogen incorporates by reference the factual background from Alvogen's § 101 Motion. (D.I. 112 at 4-8.)

IV. ARGUMENT

A. The Asserted Claims Are "Directed To" a Natural Law.

The Asserted Claims are "directed to" a natural law because the Patents-In-Suit state that their focus and only possible alleged advance relative to the prior art is the relationship between HI and the bioavailability of hydrocodone in the body after administration of certain hydrocodone ER formulations – namely, that the response of the human body to such formulations is similar in patients with and without mild or moderate HI. Unable to identify a single "focus" of the Asserted Claims, Pernix alternatively asserts they are "directed to" methods of treating pain and "the administration of non-naturally-existing compositions." (D.I. 116 at 7-

13.) Pernix, as it must, ignores the legal standard for the "directed to" inquiry, and offers no more than *ipse dixit* assertions in support of its alternate proposals.

1. The Focus and Character of the Asserted Claims as a Whole Capture a Natural Law.

Under the proper legal standard for the "directed to" inquiry, the Asserted Claims are "directed to" a natural law. They are not, as Pernix would have it, "directed to" methods of treating pain and administering a non-naturally occurring composition, and Pernix fails to offer *any* evidence in support of these different alternatives. (D.I. 116 at 7.) Indeed, Pernix's conclusory assertions come nowhere near satisfying the Federal Circuit's "directed to" standard with respect to the Asserted Claims.

In analyzing whether claims are directed to a natural law, courts must "look[] at the focus of the claims, their character as a whole." Elec. Power Grp., LLC v. Alstom S.A., 830 F.3d 1350, 1353 (Fed. Cir. 2016) (internal quotations omitted). As explained by the Federal Circuit in Enfish, which Pernix relies on in its briefing for other purposes (D.I. 116 at 6), proper identification of this focus turns on a review of the claims "in light of the specification," as well as a consideration of "the claimed advance over the prior art." Enfish, LLC v. Microsoft Corp., 822 F.3d 1327, 1335 (Fed. Cir. 2016) ("[T]he 'directed to' inquiry applies a stage-one filter to claims, considered in light of the specification"); Genetic Techs. Ltd. v. Merial L.L.C., 818 F.3d 1369, 1375 (Fed. Cir. 2016) (inquiring into "the focus of the claimed advance over the prior art"). See also Ariosa Diagnostics, Inc. v. Sequenom, Inc., 788 F.3d 1371, 1376 (Fed. Cir. 2015) ("The written description supports the conclusion that the claims . . . are directed to a naturally occurring thing or natural phenomenon.").

The specifications of the Patents-In-Suit as well as their prosecution histories establish that the true focus of the claims is an observation of how human bodies with varying degrees of

liver function metabolize HC-ER formulations. The Patents-In-Suit's specifications expressly characterize the "basic concept" of the alleged invention as the observation of this natural law:

> The ***basic concept of the invention*** can be seen when viewing FIG. 6 and understanding the results shown there. . . . The results show that although there are some differences in terms of the blood plasma levels obtained, the differences are small and the blood levels are actually very similar pharmacologically. Thus, when using a formulation of the type described here no separate dosing instructions need be given with respect to patients with and without hepatic impairment.

(Ex. 1, '760 patent at 15:36-47 (emphasis added); Ex. 2, '499 patent at 15:36-47 (emphasis added).)[2] Indeed, the Asserted Claims mirror this passage, expressing this natural law as release profiles providing certain PK values (claims 12, 17 and 19 of the '760 patent and claim 1 of the '499 patent) and non-adjustment of the starting dose (claims 1-4 and 11 of the '760 patent).[3] Pernix fails to address this critical passage in its Motion.

Pernix's Motion also ignores the prosecution histories of the Patents-In-Suit, which establishes that this same natural law, as reflected in the non-adjustment limitation, represents the only possible alleged advance relative to the prior art. Although, as explained below, this limitation is in fact conventional, the Examiner's Reasons for Allowance of the '760 patent identify it as the basis for distinguishing the prior art. (Ex. 3, PERNIX_HEP0000137.) This further demonstrates that the only conceivable advance over the prior art is premised upon the natural law relating to the bioavailability of certain HC-ER dosage forms in patients with and without mild or moderate HI. As Pernix put it, "not adjusting the starting dose is an essential limitation, if it were omitted, ***the express purpose of the invention***—administering the same

[2] Exhibit numbers refer to the Exhibits in Support of this Opposition attached to the Declaration of Christopher M. Gallo.

[3] Pernix has also stated to this Court that not adjusting the starting dose "is recited throughout the specification . . . where the applicants emphasize that . . . [not] adjusting the starting dose . . . is an essential part of the claimed invention." (D.I. 65 at 5 (citing to Ex. 1, '760 patent at 2:41-52, 7:61-8:13, 8:64-9:5, 23:39-48.)

starting dose to patients with and without [HI]—would not be fulfilled, ***rendering the other steps in the claim 'mere empty' language***." (D.I. 65 at 4-5 (emphases added).)

2. Method of Treatment Claims Are Not *Per Se* Patent-Eligible.

Rather than engage in a proper analysis of the focus of the claims in light of the specification and their alleged advance over the prior art, Pernix appears to assert that all patent claims reciting a method of treatment are *per se* patent eligible. (D.I. 116 at 7.) Pernix fails to explain why the focus of its particular Asserted Claims is a method of treatment, merely stating that "the focus must remain on the language of the claims." (D.I. 116 at 10.) Nor does Pernix explain why its claimed method of treatment represents an alleged advance over the prior art. Instead, the most Pernix offers is that the inventors "employed their discovery to create a new and improved way of treating pain in patients with hepatic impairment."[4] (Id.) That is not only beside the point because it does not meet the "directed to" standard, but as discussed below, factually inaccurate.

Pernix's assertion that courts need look no further than the recitation of a method of treatment to evaluate the "directed to" inquiry (D.I. 116 at 7-8) is wrong, because it ignores the Federal Circuit's pronouncements in Elec. Power Grp., 830 F.3d at 1353, Genetic Techs., 818 F.3d at 1375 and Enfish, 822 F.3d at 1335. Fundamentally, Pernix's failure to consider the statements in the specifications and prosecution histories of the Patents-In-Suit about the crux of the alleged invention, and its own representations to this Court, render its analysis of the "directed to" inquiry flawed.

Seeking to circumvent the proper "directed to" legal standard, Pernix advances a brand-new proposition of law – that method of treatment claims are *per se* patent eligible because they

[4] It also bears noting that the method of treatment limitation appears in the preamble, which is presumptively non-limiting and which the Court has not construed otherwise.

can never be "directed to" a natural law. (D.I. 116 at 7-11.) The case law does not support Pernix's position. Nor do the Patent Office Guidelines (which do not carry the force of law). Instead, the Patent Office Guidelines demonstrate on their face that method of treatment claims are not necessarily patent eligible.

a. Prevailing Case Law Does Not Support Pernix's New *Per Se* Rule.

Pernix cites no case, let alone a Supreme Court or Federal Circuit case, holding that method of treatment claims are *per se* patent eligible. Several courts have, on the other hand, held such claims patent ineligible. In Mayo, the Supreme Court held that claims reciting administration of an active drug to treat patients with gastrointestinal disorders was patent ineligible. Mayo Collaborative Servs. v. Prometheus Labs., Inc., 566 U.S. 66, 87 (2012). In Endo Pharms. Inc. v. Actavis Inc., C.A. No. 14-1381-RGA, 2015 WL 7253674, at *3 (D. Del. Nov. 17, 2015) ("Endo II"), this Court found methods of treating pain with the opioid oxymorphone patent-ineligible as directed to the natural law correlating the severity of renal impairment with the bioavailability of oxymorphone. Similarly, in Boehringer Ingelheim Pharms., Inc. v. HEC Pharm Co., Ltd., C.A. No. 15-5982, 2016 WL 7177704, at *7-9 (D.N.J. Dec. 8, 2016), the court found methods of treating metabolic disorders with DPP-IV inhibitors to be directed to the natural result of the body metabolizing DPP-IV inhibitors through the liver.

Rather than rebut these cases, Pernix relies heavily on dicta from Mayo, stating that the Mayo claims "were 'unlike [] a typical patent on a new drug or ***a new way of using an existing drug***, which remain patent eligible.'" (D.I. 116 at 8 (emphasis in original).) To support its position, Pernix takes this passage out of context, inaccurately portraying it as a commentary on the "directed to" inquiry of Step One. The context of the Supreme Court's statement establishes, in contrast, that it is discussing Step Two and preemption:

[H]ere, as we have said, the steps add nothing of significance to the natural laws

> themselves. Unlike, say, a typical patent on a new drug or a new way of using an existing drug, the patent claims do not confine their reach to a particular applications of those laws. The presence here of the basic underlying concern that these patents tie up too much future use of laws of nature simply reinforces our conclusion that the processes described in the patents are not patent eligible. . . .

Mayo, 566 U.S. at 87. As the full quote makes clear, the Supreme Court decided that all remaining limitations outside the natural law were conventional and that the claim improperly "tied up" or preempted the natural law. In addition, it makes clear that the Supreme Court did not create a *per se* rule that method of treatment are never "directed to" a natural law.

Further, the Asserted Claims do not even cover a new way of using an existing drug. Rather, the Asserted Claims cover using hydrocodone to treat a condition (pain) that it was already known to treat. Prior art by Jain, for example, teaches methods of treating patients with mild or moderate HI with ER hydrocodone dosage forms. (Ex. 4, Jain at ¶ 64.) The Patents In-Suit copied the claimed HC-ER formulation from Devane, which also teaches using hydrocodone to treat pain in all classes of patients. (Ex. 5, Devane at ¶¶ 70, 99-101, 104, claim 81; Ex. 6, Plaintiffs' Resp. to RFA Nos. 10, 16-18.) The Asserted Claims do not recite a new use of hydrocodone to treat HI, but merely recite the well-known use of hydrocodone to treat pain.

The dicta in CellzDirect also does not support the *per se* rule Pernix posits. (D.I. 116 at 8.) The dicta simply implies that methods of treatment, e.g., treating cancer with chemotherapy, do not qualify as directed to a natural law, but only when the subject claims are in fact "directed to" such methods of treatment. Here, the Asserted Claims are directed to the natural law reflected in the PK and no-dose-adjustment limitations – namely the relationship between the bioavailability of certain hydrocodone ER dosage forms and patients with HI. The dicta in CellzDirect is thus inapposite.

Pernix's attempt to distinguish Mayo on the basis that the Asserted Claims "amount to more than observing or identifying the ineligible concept" and do not "tie up a doctor's

subsequent treatment decision" also fails. (D.I. 116 at 8 (quoting Mayo, 566 U.S. at 75-76, 86-87).) The Asserted Claims reciting the PK limitations, without non-adjustment of the starting dose (claims 12, 17 and 19 of the '760 patent and claim 1 of the '499 patent), *do* recite nothing more than an observation premised on the natural law. The Asserted Claims reciting the non-adjustment limitation (claims 1-4 and 11 of the '760 patent) simply restate the law of nature – comparable PK values in patients with and without HI means comparable starting doses. Put another way, observation of the comparable PK values in patients with and without mild or moderate HI permits doctors to forego adjustment of the starting dose. (Ex. 16, 2003 FDA Guidance at ACT-HYD2-023067.) Further, the Mayo Court's statement regarding "tying up a doctor's treatment subsequent decision" solely concerns the Court's determination that the Mayo claims preempted use of a natural law and is not part of the Step One inquiry. That a claim may happen to recite a method of treatment does not change the result under the Step One "directed to" standard.

b. Pernix's Reliance on the Patent Office's Guidance Is Unavailing.

Perhaps recognizing that the courts have never held method of treatment claims *per se* patent-eligible, Pernix attempts to fall back on the Patent Office's non-binding Guidance. (D.I. 116 at 8-10.) The Guidance is of course not controlling law. In re Fisher, 421 F.3d 1365, 1372 (Fed. Cir. 2005) ("[t]he MPEP and [PTO] Guidelines 'are not binding on this court, but may be given judicial notice to the extent they do not conflict with the statue.'"); (See also D.I. 117-1 at 122 (citing to the 2014 IEG); Ex. 12, 2014 IEG at 79 Fed. Reg. 74619 (Dec. 16, 2014) ("[t]his Interim Eligibility Guidance does not constitute substantive rulemaking ***and does not have the force and effect of law***." (emphasis added).)

But in any event, the Guidance when read as a whole affirmatively demonstrates that method of treatment claims are not *per se* patent-eligible under on the "directed to" standard in

Step One. Specifically, claim 5 in the Guidance, which Pernix fails to address in its Brief, is similarly directed to a method for treating patients with julitis but nevertheless determined to be "directed to" a natural law. The claim provides:

> 5. A method of diagnosing and treating julitis in a patient, said method comprising:
> a. obtaining a plasma sample from a human patient;
> b. detecting whether JUL-1 is present in the plasma sample;
> c. diagnosing the patient with julitis when the presence of JUL-1 in the plasma sample is detected; and
> d. administering an effective amount of topical vitamin D to the diagnosed patient.

(D.I. 117-1 at 131-132.) According to the Guidance, claim 5 is directed to a natural law because step (c) is the "focus" of the claims. (Id. at 135.) Thus, both courts and the Patent Office agree that claims reciting methods of treatment may be "directed to" a natural law when the body of such claims focus upon the natural law.

Further, claim 5 in the Guidance is analogous to the Asserted Claims because, while the preamble recites a method of treatment, the focus is on the natural law recited in the body of the claim. Indeed, the Guidance states that the applicants' discovery resides in the natural law premised on the presence of JUL-1 in a patient's blood indicating julitis. (Id. at 130.) Just like non-adjustment of the starting dose in the Asserted Claims, the diagnosing step recited by the claim embodies the natural law, i.e., the relationship between JUL-1 in the blood and julitis.[5]

In contrast, the focus of the single step method of claim 7 from the Guidance – a method for treating julitis by administering anti-TNF antibodies – is the administering step.[6] (D.I. 116 at

[5] The Guidance states that claim 5 is patent eligible under Step Two because "the recitation of administering topical vitamin D is an unconventional step that is more than a mere instruction to 'apply' the correlation and critical thinking step (the exception) using well-understood, routine or conventional techniques in the field." (Id. at 135.) As discussed below, the Asserted Claims do not recite any additional limitations providing the requisite inventive concept under Step Two. (Infra, at 16-18.)

[6] Claim 7 from the Guidance recites "[a] method of treating a patient with julitis, the method

9.) And the reason the Patent Office characterized this claim as surviving Step One was because the administering step recited by the body of the claim was not itself a natural law. (D.I. 117-1 at 137 (citing Mayo and noting that "the recited step of administering antibodies to a patient suffering from julitis does not recite or describe any recognized exception").) Here, however, the focus of the claims is the PK and non-adjustment limitations, which are restatements of the natural law. The Guidance thus confirms that the PTO does not view method of treatment claims as *per se* "directed to" patent-eligible subject matter, and Pernix's attempt to rely on the Guidance for this proposition should be rejected.

3. Recitation of a Man-Made Drug in Claims Directed to a Natural Law Does Not Transform Such Claims Into Patent Eligible Subject Matter.

In yet another strained effort to establish that the Asserted Claims are not "directed to" a natural law, Pernix alternatively and incorrectly argues that the Asserted Claims "are directed to the administration of non-naturally-existing compositions." (D.I. 116 at 11-13.) Once again, Pernix fails to analyze the "directed to" legal standard by failing to evaluate the focus of the claims in light of the specification and their alleged advance over the prior art. Further, the Supreme Court's decision in Mayo as well as the Endo decision belie Pernix's position, and Pernix misconstrues Federal Circuit precedent.

The Asserted Claims are not "directed to administering non-naturally existing compositions." (D.I. 116 at 11-13.) Pernix spends two pages of its Brief establishing the unremarkable fact that hydrocodone is non-naturally occurring. (Id.) But Pernix offers no evidence demonstrating that the focus or character of the claims as a whole is administering an ER hydrocodone dosage form to patients with mild or moderate HI, or that hydrocodone itself

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comprising administering an effective amount of anti-TNF antibodies to a patient suffering from julitis." (D.I. 117-1 at 132.)

represents any kind of advance over the prior art. (Id.) Pernix also fails to mention the critical evidence in the specifications and prosecution histories of the Patents-In-Suit demonstrating that the basic concept of the Asserted Claims is a natural law. (See, e.g., Ex. 1, '760 patent at 15:36-47 (characterizing the natural law as the "basic concept" of the alleged invention).)

Further, the ER hydrocodone dosage form recited by the Asserted Claims cannot be the focus of the claims as the named inventors copied it from Devane. (D.I. 112 at 5.) Similarly, as discussed above, administering hydrocodone to a patient with mild or moderate HI, including administration of hydrocodone ER dosage forms to such patients, is not an alleged advance, as it was known in the prior art long before the filing of the Patents In-Suit. (Ex. 4, Jain at ¶ 64; Ex. 7, Vicodin® Label at ACT-HYD2-022214; Ex. 8, Vicoprofen® Label at ACT-HYD2-023201, ACT-HYD2-023203; Ex. 9, Lortab® Label at ACT-HYD2-022210; Ex. 10, Johnson at ACTHYD2-021165, ACT-HYD2-021170-171; Ex. 11, Smith at PERNIX_HEP0001538, PERNIX_HEP1545-547.)

Pernix's legal contentions are also wrong. Pernix ignores that the claims at issue in Mayo also recited administering non-naturally-existing compositions. In Mayo, the claims recited the step of "administering a drug providing 6-thioguanine to a subject having [an] immune-mediated gastrointestinal disorder." Mayo, 566 U.S. at 74. The compound 6-thioguanine is a synthetic purine analogue, i.e., a non-naturally-existing molecule, as is any drug metabolized into this compound in the body. (See, e.g., Ex. 13, LePage at 309, 313; Ex. 14, Bugg at 486.) Yet, the Supreme Court had no difficulty holding the claims at issue "directed to" a natural law and ultimately striking them down as patent-ineligible. Similarly, when confronted with claims reciting non-naturally existing compositions, this Court did not exempt the claims from the "directed to" inquiry of Step One. Endo II, 2015 WL 7253674 at *2-3. In Endo, the active drug

was oxymorphone, which like hydrocodone is a man-made, semi-synthetic opioid. (Ex. 15, Poyhia 1991 at 516.) As in Mayo, this Court found the claims patent-ineligible. Endo II, 2015 WL 7253674 at *2-3.

Pernix's reliance on claim 20 in Molecular Pathology is also misplaced. (D.I. 116 at 11-12 (citing Assoc. for Molecular Pathology v. U.S. Patent & Trademark Office, 689 F.3d 1303, 1336-37 (Fed. Cir. 2012), rev'd on other grounds, Assoc. for Molecular Pathology v. Myriad Genetics, Inc., 133 S. Ct. 2107 (2013).) Pernix again misconstrues the "directed to" inquiry by stating that "the inclusion of man-made cells ***alone*** rendered the claimed process patent-eligible, irrespective of whether the steps of that process were known in the art." (D.I. 116 at 12 (citing Molecular Pathology, 689 F.3d at 1336-37) (emphasis added).) Molecular Pathology is readily distinguishable. The question the Federal Circuit confronted during Step One was whether the claim was "directed to" the abstract idea of comparing DNA sequences. Molecular Pathology, 689 F.3d at 1335-36. Characterizing non-naturally occurring transformed cells as the "basis" and "heart" of the alleged invention, the Federal Circuit held that the claims were not directed to an abstract idea but rather non-naturally occurring cells. Id. at 1334-36. In other words, the basis for the Federal Circuit's holding was that the man-made material was the focus of the claims, i.e., the claims were "directed to" this subject matter. Thus, mere inclusion of man-made material in the claims, as Pernix suggests, is insufficient; rather, the alleged invention must be "directed to" such material.

Here, the Asserted Claims are directed to a natural law – the relationship between HI and the bioavailability of hydrocodone in the body after administration of certain hydrocodone ER formulations. Thus, their focus is the body's metabolism of those formulations. That they also happen to recite administering hydrocodone does not change that focus under proper application

of the governing legal standard. More specifically, the basis of the Asserted Claims is not the hydrocodone ER oral dosage form, which the named inventors copied right out of Devane.

4. Alleged "Application" of a Natural Law Does Not Change the Outcome Under Step One.

Pernix also contends that the Asserted Claims are not directed to a natural law because they recite "applications" that implement the law as opposed to mere "observations." (D.I. 116 at 10-11.) Pernix is wrong as a matter of fact. Further, Pernix cites no legal authority holding that this distinction alters the "directed to" inquiry, and Alvogen is aware of none. Thus, recitation of an application of a natural law in claims "directed to" that natural law does not salvage the Asserted Claims under Step One.

Turning first to the facts, it is beyond dispute that the wherein clauses requiring PK values, as recited by claims 2-4, 12, 17 and 19 of the '760 patent and claim 1 of the '499 patent, are observations of a natural law, and not applications of it. These clauses observe nothing more than the inherent bioavailability of hydrocodone after administration of the claimed hydrocodone ER formulations, including the prior art Devane HC-ER formulation, to HI and non-HI patients. They require no application or "subsequent treatment decision," as Pernix erroneously asserts. (D.I. 116 at 11.)

The limitation requiring non-adjustment of the starting dose in claims 1-4 and 11 of the '760 patent is similarly an observation that restates the natural law. As previously mentioned, comparable PK values means comparable starting doses. The non-adjustment limitation, in fact, comes right out of the 2003 FDA Guidance. That is, after testing the prior art Devane HC-ER formulation, the named inventors merely followed the 2003 FDA Guidance with respect to dose adjustment. (Ex. 16, 2003 FDA Guidance at ACT-HYD2-023067.) According to the FDA Guidance, dose adjustments are only necessary in HI patients when "the effect of hepatic

impairment on the PK of the drug is obvious (e.g., two-fold or greater increase in AUC). . . ." (Id.) Devane's HC-ER formulation reflected far less than a two-fold increase in AUC in patients with and without mild or moderate HI.

PK Parameters	Patients without HI	Patients with mild HI	Patients with moderate HI
$AUC_{0\text{-}inf}$	391 ng*hr/mL	440 ng*hr/mL	509 ng*hr/mL
C_{max}	22 ng/mL	24 ng/mL	25 ng/mL

(Ex. 17, Zohydro® ER Label at ALVHYDRO-PTX00013629.) Thus, the non-adjustment limitation is merely recasting the natural law in the guise of a method step. The Supreme Court long ago explained that simply because a patent claim "implements an [abstract principle or natural law] in some specific fashion" it does not "automatically fall[] within the patentable subject matter of § 101. . . ." Parker v. Flook, 437 U.S. 584, 593 (1978) (stating that determination of patentable subject matter should not "depend simply on the draftsman's art"). The Endo case illustrates this point. The claim in that case included a method step of administering a lower dose of oxymorphone – similar to the non-adjustment step here – and was nevertheless directed to the natural law relating to oxymorphone bioavailability in patients with renal impairment. Endo Pharms. Inc. v. Actavis Inc., C.A. No. 14-1381, 2015 WL 5580488, at *6 (D. Del. Sept. 23, 2015) ("Endo I"), report and recommendation adopted, Endo II, 2015 WL 7253674.

Pernix is thus left misconstruing the partial concurrence/dissent in Molecular Pathology, 689 F.3d at 1349. (D.I. 116 at 11.) The fact that Molecular Pathology states that a patentee is "free to patent applications of its discovery" does not mean all claims reciting applications of natural laws survive Step One. (Id. at 11.) Pernix takes the Court's statements in Molecular Pathology out of context. This passage did not address whether the claims were directed to a natural law, but rather addressed a separate question entirely. At issue in Molecular Pathology

were compound claims reciting naturally occurring gene sequences. Molecular Pathology, 689 F.3d at 1309, 1349. The point of the Court's statements was to note that, while the genes themselves constitute ineligible subject matter, claims properly directed to applications of such genes may be patent-eligible. Contrary to Pernix's assertion, however, Molecular Pathology does not stand for the broad proposition that all claims reciting applications of natural laws are "directed to" patent-eligible subject matter under Step One.

B. The Asserted Claims Do Not Include an Inventive Concept.

As set forth in Alvogen's § 101 Motion (D.I. 112 at 12-15), the Asserted Claims also fail Step Two because all limitations recited by the Asserted Claims, aside from the natural law itself, are conventional. Pernix's contrary argument rests on a mistake of law: namely that claim limitations reflecting natural laws may themselves serve as allegedly inventive concepts. Such is not the law. In any event, the limitations premised on the natural law are conventional, and Pernix does not even argue otherwise with respect to the PK limitations recited in claims 12, 17 and 19 of the '760 patent and claim 1 of the '499 patent. Pernix's fallback contention that "law of the case" precludes Alvogen's argument that non-adjustment of the starting dose is conventional is also wrong. The law of the case doctrine does not establish that dicta from a Markman decision on an incomplete record of the prior art binds Alvogen or the Court with respect to invalidity issues. Finally, Pernix's allegation that the administering step practically applies a product to treat pain does not make it "unconventional."

1. The Natural Law Itself Cannot Provide the Inventive Concept.

Pernix's primary basis for its assertion that the Asserted Claims recite unconventional steps improperly relies on limitations supplied by the natural law. (D.I. 116 at 13-14.) As the Federal Circuit explained, however, the "inventive concept necessary at step two [] cannot be furnished by the unpatentable law of nature [] itself." Genetic Techs., 818 F.3d at 1376. In other

words, "a claim directed to a newly discovered law of nature (or natural phenomenon or abstract idea) cannot rely on the novelty of that discovery for the inventive concept necessary for patent eligibility; instead, the application must provide something inventive, beyond mere 'well-understood, routine, conventional activity.'" Id. (citations omitted).

In Genetic Techs., the Federal Circuit found that the claims were directed to the natural law of linkage disequilibrium between coding and non-coding regions of DNA. Id. at 1376. In analyzing Step Two, the court found the remaining non-natural law elements of the claim reciting "amplifying" and "analyzing" the DNA were well-understood, routine and conventional. Id. at 1377-78. As such, even if using non-coding regions to detect coding regions of DNA could otherwise have provided an inventive concept, it could not save the claims because it was premised on the natural law of linkage disequilibrium. Id. at 1379-80.

Likewise, in Ariosa, the claims recited methods of detecting cell-free fetal DNA ("cffDNA") in maternal plasma and serum. Ariosa, 788 F.3d at 1373. The Federal Circuit found that the claims were directed to the natural phenomenon that certain DNA reside in maternal plasma and serum. Id. at 1376. In analyzing whether the claims nevertheless included an inventive concept, the Court explained that "[f]or process claims that encompass natural phenomenon, the ***process steps are the additional features that must be new and useful***." Id. at 1377 (emphasis added). Analogizing to Mayo, the Federal Circuit found that beyond reciting the natural phenomenon of cffDNA in maternal serum, the claims used "well-understood, routine, and conventional activity" by employing PCR to amplify and detect the cffDNA. Id. And the claims "amount[ed] to a general instruction to doctors to apply routine, conventional techniques when seeking to detect cffDNA" by reciting steps of preparing serum and amplifying DNA. Id. Thus, even though the claims recited steps applying the natural law, those steps were still well-

understood, routine, and conventional. Id. at 1377-78. Thus, the claims were patent ineligible.

Pernix fails to acknowledge this binding legal precedent. Indeed, the Asserted Claims, like the claims of Genetic Techs. and Ariosa, go no further in providing an inventive concept outside the natural law. All limitations of the Asserted Claims outside the natural law itself provide well-understood, routine and conventional activity – "mere empty language," according to Pernix. (D.I. 65 at 4-5.) Pernix therefore argues that administering a hydrocodone dosage unit to patients with mild or moderate HI without adjusting the starting dose and based on a PK profile enabling such dosing is unconventional. But this argument is legally flawed because it relies upon the natural law itself. (D.I. 116 at 13. (emphasis added).) Pernix's § 101 Motion does not contest that non-adjustment of the starting dose and the PK values are expressions of the natural law alleged by Alvogen. Thus, Pernix cannot, as a matter of law, rely upon these aspects to avoid Step Two and, ultimately, patent ineligibility. Ariosa, 788 F.3d at 1376-78; Genetic Techs., 818 F.3d at 1376.

Even if Pernix could rely upon these natural laws, they would not change the outcome under Step Two. The standard for determining whether a claim limitation is conventional does not require proof that the claimed method is anticipated or obvious. See Mayo, 566 U.S. at 89-90. Here, there can be no genuine dispute that the claim limitations corresponding to the natural law are routine and conventional.

a. Pernix Fails to Meaningfully Address the Claims Reciting Only PK Values in Its Mayo Step 2 Analysis.

Asserted Claims 2-4, 12, 17 and 19 of the '760 patent and claim 1 of the '499 recite release profiles requiring certain PK values achieved by administering the Devane HC-ER formulation to HI and non-HI patients. Not only are the PK values the inherent result of administering the Devane HC-ER formulation, which the named inventors did not invent, but

FDA mandated the test that led to the named inventors to report these PK values. (Ex. 18, Zogenix 30(b)(6) Deposition at 40:11-41:3, 44:23-45:2.) Further, the PK values themselves – AUC and C_{max} – were standard measures in the pharmaceutical industry for decades before the filing of the Patents-In-Suit. (See, e.g., Ex. 16, 2003 FDA Guidance at ACT-HYD-023065-068; Ex. 19, Robertson at 63; Ex. 20, Poyhia 1992 at 618-19.)

Pernix nonetheless argues that the PK values recited in Asserted Claims 2-4, 12, 17 and 19 of the '760 patent and claim 1 of the '499 patent "enable" non-adjustment of the starting dose, which thus renders them non-conventional. (D.I. 116 at 13.) But, as is clear, these claims do not even recite non-adjustment of the starting dose, the sole alleged inventive concept on which Pernix relies. (Id.) Instead, the claims simply recite the natural law itself—namely, the PK values resulting from administration of the prior art Devane HC-ER dosage form to various patient populations. The PK limitations therefore cannot serve as unconventional steps that make these Asserted Claims patent-eligible.

b. The Natural Law Concerning Non-Adjustment of the Starting Dose Does Not Render the Asserted Claims Unconventional.

Although immaterial to the Step Two analysis under a proper application of the law, Pernix also incorrectly asserts that the non-adjustment limitation, as recited in Asserted Claims 1-4 and 11 of the '760 patent, was unconventional. Non-adjustment of the starting dose is conventional because the 2003 FDA Guidance provides exactly when to do so and the named inventors did nothing more than follow its teachings. (Ex. 16, 2003 FDA Guidance at ACT-HYD2-023067; Ex. 21, PERNIX_HEP0015644.) Indeed, the labels for various commercial opioids predating the Patents In-Suit provide for non-adjustment of the starting dose in HI patients. The label for Nucynta® (tapentadol ER), for example, explicitly states that "[n]o dosage adjustment is recommended in patients with mild hepatic impairment." (Ex. 22, Nucynta® ER

Label at ACT-HYD2-023370.) Further, the label for Exaglo™ (hydromorphone ER) states to "[s]tart patients with moderate and severe hepatic . . . impairment on a reduced dose," but not those with mild HI. (Ex. 23, Exalgo™ Label at PERNIX_HEP0013311.) In addition, Jain taught that administration of an ER hydrocodone oral dosage form provided similar AUC and C_{max} in patients with and without HI, thus requiring no dose adjustment. (Ex. 4, Jain at ¶ 64.) As such, there can be no dispute that it was well-understood, routine and conventional to provide no starting dose adjustment in patients with mild and moderate HI patients relative to non-HI patients where PK levels were similar for both HI and non-HI. (Ex. 16, 2003 FDA Guidance at ACT-HYD2-023067.) That is all Pernix has done in claiming the non-adjustment limitation.

2. The Court's Markman Decision Does Not Establish Law of The Case With Respect To Patent Invalidity.

In an effort to side step the inventive concept analysis, Pernix contends that statements in this Court's Markman Order conclusively establish that the non-adjustment limitation is distinct from the prior art and unconventional. Pernix characterizes the Court's statements as "law of the case" and thus binding on Alvogen. (D.I. 116 at 16-17.) First, Pernix's argument is irrelevant because, as addressed above, claim limitations furnished by the natural law cannot supply the inventive concept. Second, Pernix is incorrect that the Court's footnote in its Markman Order constitutes law of the case.

"The 'law of the case' . . . doctrine posits that when a court decides upon a ***rule of law***, that decision should continue to govern the ***same issues*** in subsequent stages in the same case." Feesers, Inc. v. Michael Foods, Inc., 591 F.3d 191, 207 (3d Cir. 2010) (quoting Arizona v. California, 460 U.S. 605, 618 (1983)) (emphasis added). Accordingly, "[t]he law of the case doctrine is limited to issues that ***were actually decided***, either explicitly or by necessary implication, in the . . . litigation." Toro Co. v. White Consolidated Indus., Inc., 383 F.3d 1326,

1335-36 (Fed. Cir. 2004) (concluding prior claim construction was not law of the case for later analysis of the disclosure-dedication rule "[b]ecause the extent of the disclosure needed to invoke the disclosure-dedication rule was not at the crux of this court's earlier opinion") (emphasis added); see also Coca-Cola Bottling Co. of Shreveport, Inc. v. Coca-Cola Co., 769 F. Supp. 671, 703 (D. Del. 1991) ("The law of the case doctrine applies only to 'decisions' or 'rulings' of the predecessor judge. The successor judge is not bound by dicta.").

Here, the Court's footnote, and the nature of the Markman proceeding itself, establish that the Court did not actually decide the issue of whether non-adjustment of the starting dose provided an advance over the prior art, let alone whether it constituted an inventive concept under Step Two of the Mayo test. (Ex. 24, D.I. 69 at 2 n.2) Instead, the Court decided that the "wherein" non-adjustment clause was a material step of the claim in the context of claim construction. (Id.) The Court's factual observations underlying its conclusion that the nonadjustment limitation was a claim limitation have no bearing on patent-eligibility presently before the Court. Alvogen does not seek to re-litigate whether non-adjustment of the starting dose is a claim limitation in Alvogen's § 101 Motion or in the instant Opposition. Consequently, the law of the case doctrine does not foreclose the Court from concluding such non-adjustment is well-known, routine and conventional – that issue was not decided by the Court. Toro Co., 383 F.3d at 1335-36; Feesers, 591 F.3d at 207.

Pernix fails to cite a single case where dicta from a Markman decision bound the parties or court with respect to the scope and content of the prior art. The consequences of such a holding would be significant and unmanageable, and would compel litigants to include in Markman briefing every conceivable piece of prior art in order to avoid an unanticipated result in the validity phase of the case. Pernix's cases stand for the unremarkable proposition that

constructions of disputed claim limitations are law of the case, which parties cannot seek to revisit and re-construe later in the case. See, e.g., Bondyopadhyay v. United States, Case No. 14-147C, 2018 WL 798253, at *6-7 (Fed. Cl. Feb. 9, 2018) (rejecting plaintiff's attempt re-construe a claim term in a manner inconsistent with the court's claim construction in connection with infringement); Del Mar Avionics, Inc. v. Quinton Instrument Co., 836 F.2d 1320, 1324 (Fed. Cir. 1986) (finding that a claim construction determination from a prior litigation between the parties prevented redetermination of the underling facts because they remained unchanged); Anderson Corp v. Fiber Composites, LLC, 474 F.3d 1361, 1371 n.2 (Fed. Cir. 2007) (refusing to permit defendant to argue its previously rejected claim construction arguments at trial); Sprint Communs. L.P. v. Cox Communs. Inc., C.A. No. 12-487, 2017 WL 5196378, at *15-19 (D. Del. Nov. 9, 2017) (excluding expert testimony because it was contrary to the court's claim construction, and therefore, "likely to confuse the jury"); Liquid Dynamics Corp. v. Vaughan Co., 449 F.3d 1209, 1224 n.2 (Fed. Cir. 2006) (same); Gemtron Corp. v. Saint-Gobain Corp., C.A. No. 04-0387, 2008 WL 1808803, at *7-8 (W.D. Mich. Apr. 21, 2008) (refusing a jury instruction that required the jury to consider any proposed claim construction not adopted by the court).

A full reading of the Court's analysis (Ex. 24, D.I. 69 at 2-3), which Pernix selectively and misleadingly quotes, makes clear that the Court only determined whether the wherein clause reciting non-adjustment of the starting dose was a claim limitation or a non-limiting mental step. Pernix's quotations once again only tell part of the story. Indeed, the full context of the Court's statement makes very clear that the Court was evaluating the patentee's and Patent Office's statements during prosecution that the limitation allegedly distinguished the claims from the prior art. For example, the full quote characterizing non-adjustment of the starting dose as a

manipulative difference over the prior art makes clear that the Court was analyzing case law concerning wherein/whereby clauses, not the prior art as a whole, as would be expected during Markman to evaluate a patent's intrinsic evidence:

> Defendants also argue that claim phrases producing no manipulative difference in how the steps of the claims are carried out cannot be considered limitations. (D.I. 74 at 14); Minton v. Nat'l Assoc. of Sec. Dealers, Inc., 336 F.3d 1373, 1380-81 (Fed. Cir. 2003) . . . The court is not persuaded by Defendants' citations because it finds that adjusting the starting dose relative to a patient without hepatic impairment is, in fact, a manipulative difference over the prior art, not merely a statement of purpose or result.

(Ex. 24, D.I. 69 at 3.) In the end, the Court determined that non-adjustment of the starting dose was a limitation because the Applicants relied on it to differentiate the claims from the prior art during prosecution. (Id.) The Court thus had no need to make a finding that the prior art as a whole fails to teach non-adjustment of the starting dose, and certainly did not conclude that this limitation somehow represents an inventive concept. Indeed, there was no reason to do so for the limited purpose of evaluating segments of the prosecution history to decide claim construction. Pernix's truncation of the Court's statement attempts to hide this context. Moreover, neither party presented or argued the issues of patent-eligibility and validity over the prior art as a whole to the Court for the purposes of deciding whether or not the non-dose adjustment step was a limitation of the claims. As such, the law of the case doctrine does not apply for at least this additional reason. See Coca-Cola Bottling Co. of Shreveport, Inc. v. Coca-Cola Co., 988 F.2d 414, 428-30 (3d Cir. 1993) (finding that the law of the case did not apply to arguments not previously "presented and decided" in a district court's earlier opinion).

3. There is No Genuine Issue Of Fact That Administering a Well-Known Drug For a Well-Known Purpose Is Conventional.

Finally, Pernix incorrectly contends that the administering step is unconventional because it "'practically appl[ies] a product to treat a particular' condition (pain)." (D.I. 116 at 17-18.)

The act of administering simply requires delivering into the body a well-known dosage form (e.g., Devane's HC-ER) comprising a well-known active (hydrocodone) for its well-known use (treating pain). There is nothing unconventional about any of that, which is exactly why Pernix rests on conclusory argument without any explanation supporting its contention. In addition, and at bottom, whether the administering act is performed by a patient or a doctor has no bearing on the analysis because there is nothing inventive in "administering" a drug.

C. The Asserted Claims Are Broadly Preemptive

Pernix's argument that the Asserted Claims do not raise preemption concerns because they do not preempt "all uses of hydrocodone, hydrocodone oral dosage units, hydrocodone to treat pain, or even hydrocodone to treat pain in mild or moderate HI patients" (D.I. 116 at 18) misapprehends the preemption inquiry. The proper question is whether the Asserted Claims preempt ***use of the natural law***, not whether they preempt all uses of other limitations recited by the claims. See Ariosa, 788 F.3d at 1379 ("patent claims should not prevent the use of the basic building blocks of technology—abstract ideas, naturally occurring phenomena, and natural laws. While preemption may signal patent ineligible subject matter, the absence of complete preemption does not demonstrate patent eligibility").

The natural law here is the relationship between HI and the bioavailability of hydrocodone in the body after administration of certain hydrocodone ER formulations – namely that the response of the human body to such formulations is similar in patients with and without mild or moderate HI. The Asserted Claims preempt that natural law by precluding administration of any and all hydrocodone-only ER formulations that satisfy the natural law in HI patients. Pernix fails to identify utility for, or application of, the natural law that would fall outside the Asserted Claims.

Furthermore, the breadth of the natural law is not germane to the preemption

determination. The Supreme Court made clear in Mayo that preemption concerns may be quite narrow in scope. Mayo, 566 U.S. at 86 ("The laws of nature at issue here are narrow laws that may have limited applications, but the patent claims that embody them nonetheless implicate this concern."); see also Ariosa, 788 F.3d at 1379. Along these same lines, the fact that a reference by Bond discloses a single hydrocodone ER formulation that allegedly does not satisfy the non-adjustment and PK profile wherein clauses of the Asserted Claims is irrelevant. (D.I. 116 at 18.) The Asserted Claims continue to preempt all uses of all HC-ER formulations that to satisfy the PK limitations and non-adjustment limitation.

V. CONCLUSION

For the foregoing reasons, and for the reasons set forth in Alvogen's Brief in Support of Its Motion for Summary Judgment of Invalidity Under 35 U.S.C. § 101 (D.I. 112), Alvogen requests that the Court deny Pernix's Motion for Summary Judgment of No Invalidity Under 35 U.S.C. § 101, and that the Court further enter summary judgment in Alvogen's favor that the Asserted Claims are invalid under § 101.

Respectfully submitted,

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